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10/614,365	07/07/2003	Christopher J. M. Meade	01-1364	7867
28519 7590 09/09/2009 MICHAEL P. MORRIS BOEHRINGER INGELHEIM USA CORPORATION 900 RIDGEBURY RD P O BOX 368 RIDGEFIELD, CT 06877-0368				
EXAMINER OLSON, ERIC				
ART UNIT 1623		PAPER NUMBER		
NOTIFICATION DATE 09/09/2009		DELIVERY MODE ELECTRONIC		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO.e-Office.rdg@boehringer-ingelheim.com

# Office Action Summary

**Application No.**

10/614,365

**Applicant(s)**

MEADE ET AL.

**Examiner**

ERIC S. OLSON

**Art Unit**

1623

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 11 May 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,2,4,5,7-11,27-38,43 and 44 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,2,4,5,7-11,27-38,43 and 44 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **Detailed Action**

This office action is a response to applicant's communication submitted May 11, 2009 wherein claims 1, 27, and 29-38 are amended and claims 11, 13, and 19-26 are cancelled. This application claims benefit of provisional application 60/407895, filed September 3, 2002, and claims priority to foreign application DE10230769.5, filed July 9, 2002.

Claims 1, 2, 4, 5, 7-11, 27-38, 43, and 44 are pending in this application.

Claims 1, 2, 4, 5, 7-11, 27-38, 43, and 44 as amended are examined on the merits herein.

Applicant's amendment, submitted May 11, 2009, with respect to the rejection of instant claims 1, 2, 4, 5, 7-11, 13, 19-25, 28-34, 36-38, 43, and 44 under 35 USC 103(a) for being obvious over Yeadon in view of Meissner in view of Hoffman, has been fully considered and found to be persuasive to remove the rejection as the combination of references does not teach the specific pH range added to the claims. Therefore the rejection is withdrawn.

Applicant's argument, submitted May 11, 2009, with respect to the rejection of instant claims 26, 27, and 35 under 35 USC 103(a) for being obvious over Yeadon in view of Meissner in view of Hoffman in view of Dreschel, has been fully considered and found to be persuasive to remove the rejection as Dreschel is seen to be commonly

owned at the time of the invention and is therefore disqualified as prior art under 35 USC 103(c). Therefore the rejection is withdrawn.

The following new grounds of rejection are added:

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4, 5, 7-11, 27-38, 43, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yeadon et al. (US pre-grant publication 2004/0147544, of record in previous action) in view of Meissner et al., (US patent 6706726, of record in previous action, previously published in German as PCT international publication

WO02/32899 (Included with PTO-1449 12/22/2003, and German patent publication DE10050994A1, included with PTO-892) in view of Hoffman et al. (US patent 6417190, of record in previous action, first published as WO00/35428, also included with PTO-892) in view of Freund et al. (US pre-grant publication 2001/0008632, cited in PTO-892, previously published in German as PCT international publication WO98/27959, reference included with PTO-892)

Yeadon et al. discloses an inhaled combination of a selective PDE4 inhibitor and an anticholinergic agent. (p. 1 paragraph 0011) The PDE4 inhibitors include tricyclic nitrogen heterocycles that are similar in structure to the claimed PDE4 inhibitors, (p. 2 paragraph 0020) and the anticholinergics include compounds having a similar structure to those recited in instant claim 1. (p. 3 paragraphs 0049-0052) The compositions can include a pharmaceutically acceptable anion such as bromide. (p. 3 paragraph 0053) This pharmaceutical composition can be used to treat respiratory diseases including asthma, chronic or acute bronchoconstriction, chronic bronchitis, small airway obstruction, emphysema, and chronic obstructive pulmonary disease. (p. 4 paragraph 0068) The composition can be administered by inhalation as an aerosol spray either with or without a propellant. (p. 8 paragraph 0112) For use in an atomizer, the composition can be prepared as a solution containing the active compounds, propylene glycol, (a co-solvent according to instant claims 30-31) sterile water, ethanol, and sodium chloride. (p. 8 paragraph 0114) The overall dose of the active substances is preferably between 1 µg and 20 mg. (p. 9 paragraph 0115) The ratio of the two agents

to one another will be determined by the potency of the individual compounds being used. (p. 9 paragraph 0116)

Yeadon et al. does not disclose a pharmaceutical combination comprising the specific anticholinergics and PDE-4 inhibitors recited in instant claim 1. Yeadon et al. also does not disclose compositions having the exact doses and ratios of active substances recited in instant claims 8-11 or a propellant-free inhalable solution having a pH of between 2 and 7 or 2 and 5. Yeadon et al. does not disclose a composition comprising an antioxidant such as ascorbic acid, vitamin A, vitamin E, or tocopherol.

Meissner et al. discloses anticholinergic compounds of a general formula which includes 1 as an embodiment. (Example 1, column 10, lines 10-29) These agents are expected to be useful in the treatment of chronic obstructive pulmonary disease and asthma. (column 19, lines 63-65) Meissner et al. specifically discloses that these compounds may be administered by inhalation. (column 22, lines 26-29) Specific formulations described by Meissner et al. include an aerosol spray for use in an inhaler, (column 24, lines 40-55) an inhalable solution according to instant claims 25-29, 32, 33, 36, and 39 for use in an inhaler according to instant claim 42, (column 24, lines 58-67) and a powder comprising the active substance and lactose monohydrate. (column 25, lines 15-20)

Hoffmann et al. discloses tricyclic heterocycles that are selective PDE-4 inhibitors. (column 2 lines 8-12) These compounds have the same structure **2a** recited in the instant claims. (column 2 lines 2-46) These compounds can be used as their physiologically acceptable salts by the addition of inorganic or organic acids, including

acids such as succinic, hydrobromic, acetic, fumaric, maleic, methanesulfonic, hydrochloric, and other acids recited in instant claim 28. (column 3 lines 22-30)

Solutions of these compounds can contain preservatives such as p-hydroxybenzoates, and stabilizers such as alkali metal salts of EDTA. (column 5 lines 58-62) A therapeutically effective dose is between 10-300 mg. (column 6 lines 4-6)

Freund et al. discloses aqueous solutions for the production of propellant-free aerosols for inhalation. (p. 1 paragraph 0001) The compositions are dissolved in aqueous or ethanolic solution. (p. 1 paragraph 0004) Active agents that can be included in these solutions include anticholinergics of similar structure to the claimed compounds, for example tiotropium bromide, ipratropium bromide, oxitropium bromide, and trospium chloride. (p. 1 paragraph 0014 - p. 2 paragraph 0023) In one embodiment a solution of ipratropium bromide is used having a pH of 3.4, with benzalkonium chloride as a preservative. (p. 2 paragraph 0048) In this example the solution can contain no further or ingredients in one embodiment, or optionally can contain sodium EDTA. In another embodiment the solution contains HCl to adjust the pH. (p. 3 paragraph 0050) Also note that a solution of benzalkonium chloride at pH 3.4 contains both  $H^+$  ions and  $Cl^-$  ions, and therefore is reasonably considered to contain small amounts of hydrochloric acid even without the addition of exogenous HCl. Freund et al. also discloses solutions containing ascorbic acid as a complexing agent. (p. 1 paragraph 0011)

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce a composition similar to those disclosed by Yeadon et al.

comprising the anticholinergic drug of Meissner et al. in place of the anticholinergics disclosed by Knowles et al and to use this combination in the therapeutic method of claim 43. It would also have been obvious to one of ordinary skill in the art to prepare this composition as a propellant-free inhalable aerosol as described in claims 25-39.

One of ordinary skill in the art would have been motivated to prepare the composition using the anticholinergic compound 1 of Meissner et al. in place of the anticholinergics of Knowles et al. because this compound is also an anticholinergic, is structurally similar to the compounds of Yeadon et al., and is useful for treating the same condition. (i.e. obstructive pulmonary disease) Similarly one of ordinary skill in the art would have been motivated to use the PDE-IV inhibitors of Hoffman et al. because they have the same function and closely similar structure to those used by Yeadon et al. One of ordinary skill in the art would have been motivated to prepare an aerosol containing additional ingredients as described by claim 23 because adding standard ingredients such as preservatives, stabilizers, and surfactants is standard practice in the art. One of ordinary skill in the art would have been motivated to prepare the composition as a propellant-free aerosol because Meissner et al. discloses such a solution as a means for pulmonary delivery of the anticholinergic, and because Yeadon et al. also discloses such a solution for use in an atomizer. One of ordinary skill in the art would have been motivated to use sodium EDTA in this solution because Meissner et al. discloses a solution comprising EDTA and sodium EDTA is a common form of EDTA. One of ordinary skill in the art would have been motivated to prepare the solution with only benzalkonium chloride or benzalkonium chloride and sodium EDTA



because these solutions consist essentially of the same ingredients as the propellant-free solution disclosed by Meissner et al. and differ only in the absence of HCl, which is not essential to the biological function of the active ingredient.

One of ordinary skill in the art would have reasonably expected success in preparing the pharmaceutical composition with the compounds of Meissner et al. and Hoffman et al. because of the similarities between these compounds and those already known to be useful in this invention. One of ordinary skill in the art would have been motivated to make various minor modifications such as adding ingredients as described by claims 23, 30, 31, and 34 or subtracting them as described in instant claims 18, 36, and 37 because these modifications are minor modifications which are well within the routine skill of one of ordinary skill in the art. Furthermore choosing specific amounts and ratios of the disclosed compounds, as described by Yeadon et al. above, is similarly within the ordinary level of skill in the art.

It would also have been obvious for one of ordinary skill in the art at the time of the invention to prepare the compositions of Yeadon et al. in view of Meissner et al. in view of Hoffman et al. as propellant-free solutions according to Freund et al. having a pH of 3.4, and containing ascorbic acid. One of ordinary skill in the art would have been motivated to use this pH and complexing agent because Yeadon et al. in view of Meissner et al. in view of Hoffman et al. already discloses inhalable formulations including propellant-free solutions, which are similar to those described by Freund et al. to also be used for inhalation of therapeutic agents. One of ordinary skill in the art would reasonably have expected success because the formulation of Freund et al. is

already disclosed to be useful for delivery of pharmaceutical ingredients by inhalation, particularly anticholinergics.

Therefore the invention taken as a whole is *prima facie* obvious.

Claims 1, 2, 4, 5, 7-11, 27-38, 43, and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yeadon et al. (US pre-grant publication 2004/1047544, of record in previous action) in view of Meissner et al., (US patent 6706726, of record in previous action, previously published in German as PCT international publication WO02/32899, included with PTO-1449 December 22, 2003, and German patent publication DE10050994A1, included with PTO-892) in view of Hoffman et al. (US patent 6417190, of record in previous action, first published as WO00/35428, also included with PTO-892) in view of Hochrainer et al. (Foreign patent publication CA2345675, reference included with PTO-892, also published as US pre-grant publication 2001/0032643, cited in PTO-892)

Yeadon et al. discloses an inhaled combination of a selective PDE4 inhibitor and an anticholinergic agent. (p. 1 paragraph 0011) The PDE4 inhibitors include tricyclic nitrogen heterocycles that are similar in structure to the claimed PDE4 inhibitors, (p. 2 paragraph 0020) and the anticholinergics include compounds having a similar structure to those recited in instant claim 1. (p. 3 paragraphs 0049-0052) The compositions can include a pharmaceutically acceptable anion such as bromide. (p. 3 paragraph 0053) This pharmaceutical composition can be used to treat respiratory diseases including asthma, chronic or acute bronchoconstriction, chronic bronchitis, small airway

obstruction, emphysema, and chronic obstructive pulmonary disease. (p. 4 paragraph 0068) The composition can be administered by inhalation as an aerosol spray either with or without a propellant. (p. 8 paragraph 0112) For use in an atomizer, the composition can be prepared as a solution containing the active compounds, propylene glycol, (a co-solvent according to instant claims 30-31) sterile water, ethanol, and sodium chloride. (p. 8 paragraph 0114) The overall dose of the active substances is preferably between 1  $\mu\text{g}$  and 20 mg. (p. 9 paragraph 0115) The ratio of the two agents to one another will be determined by the potency of the individual compounds being used. (p. 9 paragraph 0116)

Yeadon et al. does not disclose a pharmaceutical combination comprising the specific anticholinergics and PDE-4 inhibitors recited in instant claim 1. Yeadon et al. also does not disclose compositions having the exact doses and ratios of active substances recited in instant claims 8-11 or a propellant-free inhalable solution having a pH of between 2 and 7 or 2 and 5 according to instant claims 26 and 27. Yeadon et al. does not disclose a composition having a pH range of between 2-5 or a composition comprising an antioxidant such as ascorbic acid, vitamin A, vitamin E, or tocopherol.

Meissner et al. discloses anticholinergic compounds of a general formula which includes 1 as an embodiment. (Example 1, column 10, lines 10-29) These agents are expected to be useful in the treatment of chronic obstructive pulmonary disease and asthma. (column 19, lines 63-65) Meissner et al. specifically discloses that these compounds may be administered by inhalation. (column 22, lines 26-29) Specific formulations described by Meissner et al. include an aerosol spray for use in an inhaler,

(column 24, lines 40-55) an inhalable solution according to instant claims 25-29, 32, 33, 36, and 39 for use in an inhaler according to instant claim 42, (column 24, lines 58-67) and a powder comprising the active substance and lactose monohydrate. (column 25, lines 15-20)

Hoffmann et al. discloses tricyclic heterocycles that are selective PDE-4 inhibitors. (column 2 lines 8-12) These compounds have the same structure **2a** recited in the instant claims. (column 2 lines 2-46) These compounds can be used as their physiologically acceptable salts by the addition of inorganic or organic acids, including acids such as succinic, hydrobromic, acetic, fumaric, maleic, methanesulfonic, hydrochloric, and other acids recited in instant claim 28. (column 3 lines 22-30) Solutions of these compounds can contain preservatives such as p-hydroxybenzoates, and stabilizers such as alkali metal salts of EDTA. (column 5 lines 58-62) A therapeutically effective dose is between 10-300 mg. (column 6 lines 4-6)

Hochrainer et al. discloses a two-chamber inhaler device containing a powdered active agent and a liquid solvent, wherein the active agent is dissolved in the solvent before use. (p. 3 paragraphs 3-4) Preferred solvents are propellant-free liquids including water, ethanol, and mixtures thereof. (p. 16 lines 2-14) In one embodiment EDTA or sodium EDTA is added. (p. 16 last paragraph) In another preferred embodiment the pH is between 3.0 and 4.0, adjusted by the addition of hydrochloric acid. (p. 17 second paragraph) Vitamins including ascorbic acid and vitamin E can be included as antioxidants. (p. 13 fifth paragraph) Specific examples of active agents that can be

administered in this manner include tiotropium bromide, ipratropium bromide, oxitropium bromide, and tropium chloride. (p. 8)

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce a composition similar to those disclosed by Yeadon et al. comprising the anticholinergic drug of Meissner et al. in place of the anticholinergics disclosed by Knowles et al and to use this combination in the therapeutic method of claim 43. It would also have been obvious to one of ordinary skill in the art to prepare this composition as a solvent-free inhalable aerosol as described in claims 25-39.

One of ordinary skill in the art would have been motivated to prepare the composition using the anticholinergic compound 1 of Meissner et al. in place of the anticholinergics of Knowles et al. because this compound is also an anticholinergic, is structurally similar to the compounds of Yeadon et al., and is useful for treating the same condition. (i.e. obstructive pulmonary disease) Similarly one of ordinary skill in the art would have been motivated to use the PDE-IV inhibitors of Hoffman et al. because they have the same function and closely similar structure to those used by Yeadon et al. One of ordinary skill in the art would have been motivated to prepare an aerosol containing additional ingredients as described by claim 23 because adding standard ingredients such as preservatives, stabilizers, and surfactants is standard practice in the art. One of ordinary skill in the art would have been motivated to prepare the composition as a propellant-free aerosol because Meissner et al. discloses such a solution as a means for pulmonary delivery of the anticholinergic, and because Yeadon et al. also discloses such a solution for use in an atomizer. One of ordinary skill in the

art would have been motivated to use sodium EDTA in this solution because Meissner et al. discloses a solution comprising EDTA and sodium EDTA is a common form of EDTA. One of ordinary skill in the art would have been motivated to prepare the solution with only benzalkonium chloride or benzalkonium chloride and sodium EDTA because these solutions consist essentially of the same ingredients as the propellant-free solution disclosed by Meissner et al. and differ only in the absence of HCl, which is not essential to the biological function of the active ingredient.

One of ordinary skill in the art would have reasonably expected success in preparing the pharmaceutical composition with the compounds of Meissner et al. and Hoffman et al. because of the similarities between these compounds and those already known to be useful in this invention. One of ordinary skill in the art would have been motivated to make various minor modifications such as adding ingredients as described by claims 23, 30, 31, and 34 or subtracting them as described in instant claims 18, 36, and 37 because these modifications are minor modifications which are well within the routine skill of one of ordinary skill in the art. Furthermore choosing specific amounts and ratios of the disclosed compounds, as described by Yeadon et al. above, is similarly within the ordinary level of skill in the art.

It would also have been obvious for one of ordinary skill in the art at the time of the invention to prepare the compositions of Yeadon et al. in view of Meissner et al. in view of Hoffman et al. as propellant-free solutions according to Hochrainer et al. having a pH of 3.0-4.0. One of ordinary skill in the art would have been motivated to do so because Yeadon et al. in view of Meissner et al. in view of Hoffman et al. already

discloses inhalable formulations including propellant-free solutions, which are similar to those described by Hochrainer et al. to also be used for inhalation of therapeutic agents. One of ordinary skill in the art would reasonably have expected success because the formulation of Hochrainer et al. is already disclosed to be useful for delivery of pharmaceutical ingredients by inhalation, particularly anticholinergics.

Therefore the invention taken as a whole is *prima facie* obvious.

### **Conclusion**

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERIC S. OLSON whose telephone number is (571)272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Eric S Olson/  
Examiner, Art Unit 1623  
9/1/2009